and 15 are dependent from claim 9 and are directed to the further use of chemotherapeutic agents.

All claims 1, 7-10, 14 and 15 were rejected under 35 U.S.C. § 112, first paragraph as assertedly lacking enablement for *in vivo/* therapeutic applications. It was the Examiner's position that the specification was only enabling for *in vitro* methods and did not enable therapeutic *in vivo* application of antisense oligonucleotides for modulation of the cell cycle, cell proliferation, and cytokinesis. The Examiner acknowledged that the specification as filed provided guidance for inhibiting survivin expression in cells in culture, and that Example 25 in the specification indicated that anti-survivin antisense oligonucleotides reduced survivin levels in human skin grafts in immunodeficient mice. However, the Examiner expressed concern that Example 25 did not show the level of survivin reduction or statistical significance. The Examiner suggested that the art of nucleic acid based therapy is generally unpredictable, citing Jen, *Stem Cells*, 18:307-319 (2000) ("Jen") and Branch, *TIBS* 23:45-50 (1998) ("Branch"). The Examiner also asserted that it was not clear how survivin level reduction correlated to the treatment of disease states with survivin targeted antisense.

Applicants respectfully submit that one of ordinary skill in the art would be able to carry out the claimed methods without undue experimentation. The claimed methods do not require the cure of any particular disease state but rather are directed to inhibiting survivin expression, modulating cytokinesis, modulating the cell cycle, and inhibiting cell proliferation. Applicants have demonstrated each of these effects in the specification as filed. Applicants' data show that anti-survivin antisense oligonucleotides reduce survivin expression, block cytokinesis, and inhibit cell proliferation in cancerous cells *in vitro*, and moreover that anti-survivin antisense oligonucleotide reduces survivin expression *in vivo*. See, e.g., Examples 21-23 and 25. The Examiner has not identified specific reasons why these data are not believeable, or why it would require undue experimentation to achieve the effects demonstrated. Although the Examiner stated that Example 25 did not show the level of survivin reduction or statistical significance, there is no legal requirement that Applicants must show the figures and statistics underlying the stated results or that statistical significance is required.

The Examiner's concern regarding unpredictability of nucleic acid based therapy appears misplaced because the cited articles, Jen and Branch, simply discuss theoretical reasons why antisense drugs *might* not be effective and do not apply to the present situation where Applicants have demonstrated that the antisense drug *is* effective in reducing levels of expression. Thus, for example, the discussion in Branch of the potential inaccessibility of target mRNA, and the discussion in Jen regarding selecting accessible mRNA sites, delivering antisense drug into cells, and localizing the antisense agent intracellularly to the same cellular compartment as the target mRNA, are not relevant considerations here. The data in Example 25 showed that survivin expression in the human skin grafts treated with anti-survivin antisense oligonucleotide was downregulated compared to the grafts treated with control oligonucleotide, indicating that the anti-survivin antisense oligonucleotide was effective and that the effect was specific to the targeting of survivin. In addition, the data in Example 25 showed that downregulation was observed in both dermal microvessels and epidermal keratinocytes, even though the agent was administered topically and was not directly administered into the blood vessels, indicating that delivery to the cells was readily achieved.

The Examiner's citation of Branch for the possibility of non-antisense side effects and a narrow therapeutic index is also not a sufficient reason why one of ordinary skill in the art would be unable to carry out the claimed methods to obtain the desired beneficial effect. Almost all drugs have some side effects; anti-cancer drugs in particular have very toxic side effects and narrow therapeutic windows, yet this does not prevent practitioners from using such drugs.

The Examiner's concern that it was not clear how survivin level reduction correlated to the treatment of disease states with survivin targeted antisense is not believed to be relevant to the presently pending claims, which do not require the cure of any particular disease states. Nevertheless, Applicants respectfully note that the specification shows that reduction of survivin levels through administration of anti-survivin antisense resulted in an inhibition of cytokinesis and cell proliferation in cancerous cells. Thus, the reduction of survivin levels has been shown to be correlated to the inhibition of proliferation and is expected to be beneficial in a variety of diseases including cancer. The specification states

that there are a number of reports indicating that survivin is overexpressed in a wide variety of cancers, including lung, colon, pancreas, prostate, breast, stomach, non-Hodgkin's lymphoma, and neuroblastoma and that higher expression levels are correlated with poor prognosis. See, e.g., page 2, lines 12-34.

The present situation is analogous to *In re Chilowsky*, 108 USPQ 321, 325 (CCPA 1956), in which the Court of Customs and Patent Appeals (the predecessor to the Federal Circuit) stated that:

> We do not consider that a broad allegation that the application disclosure is speculative, coupled with a recitation of various difficulties which might be encountered in attempting to put it into practice, and a further assertion that there might be still other difficulties which could not be foreseen, constitutes a sufficiently definite statement of a basis for rejection.

In this case, as in Chilowsky, the Patent Office's statements simply do not constitute a "sufficiently definite statement of a basis for rejection."

CONCLUSION

For these reasons, Applicants respectfully submit that all pending claims 1, 7-10, 14 and 15 are allowable. Reconsideration of the outstanding rejection is respectfully requested and an early notice of allowance is solicited.

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Respectfully submitted,

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